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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 02262004

Application Number: 09/895,686
Filing Date: June 28, 2001
Appellant(s): BANDMAN ET AL.

David G. Streeter, Ph.D
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 09 January 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is essentially correct, except that the asserted utilities for the claimed invention are currently being disputed.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes statements that claims stand or fall together but does not provide reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) ***Prior Art of Record***

WO 99/55721	Valenzuela et al.	11-1999
U.S. 20030055236	Moore et al.	03-2003
5,194,596	Tischer et al.	03-1993
5,350,836	Kopchik et al.	09-1994

Ji et al. (1998), The Journal of Biological Chemistry Vol. 273, No. 28, pp.17299-17302.

Vukicevic et al. (1996), PNAS USA Vol. 93, pp. 9021-9026.

Sen (2000), Current Opinion in Oncology, Vol. 12, pp. 82-88.

Stryer, (1991), J. Biol. Chem., Vol. 266, pp. 10711-10714.

Watson and Arkinstall, (1991), The G-Protein Linked Receptor Facts Book, Academic Press, San Diego, CA., pp. 2-6, 130-132, 278-283.

(10) ***Grounds of Rejection***

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-6 are rejected under 35 U.S.C. 101. This rejection is set forth in prior Office Actions, Paper No. 9 and 11.

Claim Rejections - 35 USC § 101

Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 1-6 are directed to isolated cDNAs encoding the amino acid sequence of SEQ ID NO: 1, variants thereof, vectors comprising same, host cells comprising the vectors, and methods of recombinantly producing the encoded polypeptides, or the complement of the encoding nucleic acid sequence, or cDNA comprising the nucleotide sequence of SEQ ID NO: 7. The

instant specification discloses that the polypeptide comprising the amino acid sequence presented in SEQ ID NO:1 is presumably a member of the G-protein coupled receptor (GPCR) superfamily identified as a metabotropic GPCR, based on homology to that family of proteins. However, the protein and encoding nucleic acids do not have any specific and substantial utility, or a well established utility, as determined according to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday, January 5, 2001.

The specification describes the uses and methods of the invention, in which the proteins and nucleic acids can be used in methods such as screening assays to identify ligands and binding compounds, methods to inhibit or regulate expression of the nucleic acid or polypeptide, use of the nucleic acids as probes to identify orthologs or related genes from the same species or to screen cDNA libraries or genomic libraries, to make transgenic or knock out animals to produce mammalian model systems, to raise monoclonal or polyclonal antibodies, to detect the differential expression of a nucleic acid in a sample, to make a microarray, or to identify chromosomes or location of particular sites on a chromosome, or to express the nucleic acid in order to make the protein.

However, none of these uses are considered to be specific or substantial utilities for either the protein or the encoding nucleic acid molecules. Methods such as identification of ligands, use to screen for homologous genes, use in microarrays, use to identify chromosomes or chromosomal location, use to recombinantly produce protein or use to generate antibodies are considered general methods applicable to any protein and/or nucleic acid, and are not considered specific or substantial.

The instant application also teaches that the nucleic acids, proteins and associated

antibodies and antisense nucleic acids can be used to can be used either diagnostically to detect abnormal levels of the protein or nucleic acids and associated disorders or diseases, or therapeutically to treat diseases or disorders, such as infection, inflammation and cancer, and particularly meningioma of the brain. However, the assertion that the protein and/or nucleic acids of the instant invention can be used in the diagnosis or treatment of diseases or disorders is also not a specific and substantial utility, and is based on the fact that the cDNA encoding the human receptor of SEQ ID NO: 1 was first identified from a brain meningioma cDNA library.

Applicants provide information from transcript images on pages 34-35, in which cDNA libraries from different tissues were assayed for abundance of the nucleic acid of SEQ ID NO: 7. From this information, Applicant's state that SEQ ID NO: 7 was differentially expressed in follicular carcinoma of the thyroid and expression was 4-fold higher than in any other thyroid tissue. Applicants also state that the sequence was not expressed in cytologically normal thyroid (5 libraries), lymphocytic thyroiditis (2 libraries), hyperthyroidism, goiter or papillary carcinoma. Also, the assertion that the nucleic acid molecule can be used diagnostically is based on the result from two different cancer cell line libraries and a single pre-cancerous cell line library. The skilled artisan would not find it more likely than not that this nucleic acid could be used diagnostically to detect follicular carcinoma of the thyroid based on a slight increase in expression of the gene from libraries from three different cell lines. Further, over expression of a given sequence in a single isolate would not be considered by a person of ordinary skill in the art to be predictive of diagnostic utility for that type of tumor. Thus, the data do not support the implicit assertion that the nucleic acid can be used as a cancer diagnostic. Significant further research would have been required of the skilled artisan to determine whether the nucleic acid

molecule of SEQ ID NO: 7 is over expressed in any cancer to the extent that it could be used as a cancer diagnostic, and thus the asserted utility is not substantial.

Claim Rejections - 35 USC § 112

Claims 1-6 are rejected under 35 U.S.C. 112, for lack of enablement. This rejection is set forth in prior Office Actions, Paper No. 9 and 11.

Claims 1-6 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 1 and 3-6 are rejected under 35 U.S.C. 112, first paragraph, for lack of written description. This rejection is set forth in prior Office Action, Paper No. 11.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification describes a polypeptide sequence consisting of SEQ ID NO: 1. However, the claims as written include polypeptides comprising fragments and homologues, encompass polypeptides that vary substantially in length and also in amino acid composition. The instant disclosure of a single polypeptide, that of SEQ ID NO: 1, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of*

the University of California v Eli Lilly & Co, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polypeptide sequence SEQ ID NO: 1. Protein function, however, cannot be reliably predicted from protein sequence homology. For example, Transforming Growth Factor (TGF-beta) Family OP-1 induces metanephrongenesis whereas closely related TGF-beta family members-BMP-2

and TGF-beta1-have no effect on metanephrogenesis under identical conditions (Vukicevic et al., 1996, PNAS USA 93:9021-9026). Platelet-derived Growth Factor (PDGF) Family VEGF, a member of the PDGF family, is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells while PDGF is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (Tischer et al., U.S. Patent 5,194,596, column 2, line 46 to column 3, line 2). Finally, vertebrate growth hormone of 198 amino acids becomes an antagonist (inhibitor of growth) when a single amino acid is changed (Kopchick et al, U.S. Patent No. 5,350,836). Even 99% homology does allow predictability in this instance. Given the unpredictability of homology comparisons, and the fact that the specification fails to provide objective evidence that the additional sequences are indeed species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim. No activity is set forth for the additional sequences. The instantly claimed genus is not so limited and the prior art does not provide compensatory structural or correlative teachings to enable one of skill to identify the polynucleotides encompassed.

Priority Determination

35 U.S.C. § 120 states that:

> An application for patent for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States, or as provided by section 363 of this title, which is filed by an inventor or inventors named in the previously filed application shall have the same effect, as to such invention, as though filed on the date of the prior application, if filed before the patenting or abandonment of or termination of proceedings on the first application or on an application similarly entitled to the benefit of the filing date of the first application and if it contains or is amended to contain a specific reference to the earlier filed application.

The instant application can only receive benefit under 35 U.S.C. § 120 from an earlier application which meets the requirements of 35 U.S.C. § 112, first paragraph, which respect to the now claimed invention. Because the instant application does not meet the requirements of 35 U.S.C. § 112, first paragraph, for those reasons give above and it is a continuation of application Serial Number 09/516,513, the prior application does not meet those requirements and, therefore, is unavailable under 35 U.S.C. § 120. The effective priority date of the instant application is considered to be the filing date of this application, June 28, 2001, because the claimed invention is not supported by either a specific and substantial utility or a well established utility.

Claim Rejections - 35 USC § 102

Claims 1 and 3-6 are rejected under 35 U.S.C. 102(b). This rejection is set forth in prior Office Action, Paper No. 9 and 11.

Claims 1 and 3-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Valenzuela et al., WO 99/55721, Nov. 4, 1999.

Claims 1 and 3-6 encompass an isolated cDNA comprising a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 1, vector and host cell comprising the cDNA, method of using the cDNA to produce the encoded protein, and composition comprising the cDNA and a labeling moiety.

Valenzuela et al. disclose a nucleic acid molecule (SEQ ID NO: 43, claim 52) that encodes a protein (SEQ ID NO: 45, claim 53) that is 100% identical to the polypeptide of SEQ ID NO: 7 of the instant application. Valenzuela et al. also teach vectors (Figures 1A and 1B),

host cells (pages 137 and 146), method of producing protein (pages 246-147) and labeled DNA (page 149). Therefore, Valenzuela et al. anticipates the claims.

Claims 1 and 3-6 are rejected under 35 U.S.C. 102(b). This rejection is set forth in prior Office Action, Paper No. 11.

Claims 1 and 3-6 are rejected under 35 U.S.C. 102(e) as being anticipated by Moore et al., U.S. Published Application 20030055236, effective filing date June 17, 1999 (divisional of 09/334,595).

Claims 1 and 3-6 encompass an isolated cDNA comprising a nucleic acid encoding a fragment of SEQ ID NO: 1 from I51-V72, G88-V109, C116-A145, I156-L175, M207-P229 or G242-T264 of SEQ ID NO: 1, vector and host cell comprising the cDNA, method of using the cDNA to produce the encoded protein, and composition comprising the cDNA and a labeling moiety.

Moore et al. disclose a nucleic acid molecule (SEQ ID NO: 22) that encodes a protein (SEQ ID NO: 146) that is 100% identical to the polypeptide of SEQ ID NO: 1 from amino acids 1-384 of the instant application, and therefore discloses an isolated cDNA comprising a nucleic acid encoding a fragment of SEQ ID NO: 1 from I51-V72, G88-V109, C116-A145, I156-L175, M207-P229 or G242-T264 of SEQ ID NO: 1. Moore et al. also teach vectors (claim 7), host cells (claims 9-10) method of producing protein (claim 15) and labeled DNA (paragraphs 1078, 1080 and 1238). Therefore, Moore et al. anticipates the claims.

(11) Response to Argument

At p. 4, last paragraph of the Brief, Appellant characterizes the invention as a polynucleotide sequence corresponding to a gene that is expressed in human tissues and that codes for a polypeptide which is a member of the class of glutamate GPCRs (G-protein coupled receptors) whose biological functions include control of neurotransmission. Appellant urges that the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development and diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the claimed polynucleotide actually functions.

Appellant states that the claimed invention already enjoys significant commercial success. This has been fully considered but is not found to be persuasive for several reasons. Although the specification on page 35 presents data that the levels of the polynucleotides are increased in thyroid cancers and asserts that the polynucleotides can be used in the detection and diagnosis of cancer, this is not found persuasive and is discussed later in the response to this assertion on page 28 of the Brief. Therefore, the claimed genes are not markers for specific diseases. Absent a correlation between altered levels or forms of a gene in diseased tissue as compared with the corresponding healthy tissue, the gene is not a disease marker or an appropriate target for drug discovery or toxicology testing. Finally, evidence of commercial success, while sometimes persuasive as secondary evidence of non-obviousness, is immaterial to utility and enablement. Many products have enjoyed commercial success due to fads or clever advertising, wherein the products would not have met the legal standards for utility and enablement.

Beginning at p. 5, second paragraph, Appellants discuss the previously submitted Rockett declaration, and characterize the Rockett declaration as describing some of the practical uses of the claimed invention in gene expression profiling studies in toxicology testing, and submit that such a used would be readily apparent to the skilled artisan at the time the application was filed. At page 5, third paragraph, Appellants discuss the declarations by Dr. Iyer and Dr. Bedilion submitted with the Brief under 37 CFR 1.132, and ten scientific references filed before Sept. 17, 1998, the priority date of the instant application. On pages 5-6, Appellants characterize the Rockett, Iyer and Bedilion declarations, and the ten references, as describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications, thus allegedly demonstrating the examiner's position to be without merit. Beginning at the bottom of p. 6 of the Brief, Appellants criticize the examiner's position that the claimed polynucleotide cannot be useful without precise knowledge of its biological function. However, Appellant is mischaracterizing the examiner's position. A specification can meet the legal requirements of utility and enablement for a new polynucleotide as long as the specification discloses a credible, specific and substantial asserted utility for the new polynucleotide, or a well-established utility for the claimed polynucleotide. A hypothetical example may serve to clarify. For example, a hypothetical specification discloses that a claimed polynucleotide is closely linked chromosomally to a known disease, and that there is a restriction fragment length polymorphism for the polynucleotide which co-segregates with the disease. Therefore, the polynucleotide may be used to detect individuals carrying the disease gene. The hypothetical specification does not disclose the biological activity of the polypeptide encoded by the polynucleotide. The claimed polynucleotide in the hypothetical example would not be rejected

under 35 U.S.C. §§ 101 and 112, first paragraph, as it has utility and is enabled as a disease marker. However, such is not the fact pattern here. The instant specification discloses that the claimed polynucleotides encode a protein that is structurally related to glutamate GPCRs and hypothesizes that the protein is involved in control of neurotransmission. There is no sufficient disclosure that the claimed polynucleotides are expressed at altered levels or forms in any specific, diseased tissue. Also, no evidence has been brought forth that the claimed polynucleotides encode polypeptides having specific receptor activities.

I. The applicable legal standard

Beginning at p. 7 of the Brief, Appellants summarize case law on the utility requirement. The essential disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility, as will be explained more fully below.

II. Toxicology testing, and disease diagnosis are alleged to be sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

A. The use of the claimed SEQ ID NO: 1 encoding polypeptides for toxicology testing, drug discovery, and disease diagnosis are alleged as practical uses that confer specific benefits to the public.

Appellants argue at pages 9-11 of the Brief that the use of the polynucleotide of SEQ ID NO: 1 for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer specific benefits to the public. Appellants state that there is no dispute that the claimed invention is a useful tool in cDNA microarrays used to perform gene expression analysis. Appellants

assert that such is sufficient to establish utility for the claimed polynucleotide. This is not found to be persuasive. While the examiner agrees that any polynucleotide, including the claimed polynucleotides, can be used in a cDNA microarray, such does not confer patentable utility on the claimed polynucleotides. Since any polynucleotide can be used in a microarray, such a use is not specific to the claimed polynucleotides. Just as any orphan receptor can be used in an assay to screen for ligands, such does not confer patentable utility on a particular orphan receptor. Such can be done with any orphan receptor, and thus the asserted utility is not specific. Furthermore, since the specification does not disclose a persuasive correlation between any disease or disorder and an altered level or form of the claimed polynucleotides, the results of gene expression monitoring assays would be meaningless without significant further research. Therefore, the asserted utility is also not substantial.

On page 9, Appellants refer to the Bedilion declaration as explaining the many reasons why a person skilled in the art reading the instant application would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, such as a probe for expression of the polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. The Bedilion declaration discusses microarrays and Northern analysis for measuring such. Specifically, Appellants quote from the Bedilion declaration that a person skilled in the art would have been able to use the claimed polynucleotide in expression profiling studies in toxicology. This is not found to be persuasive. The instant specification does not substantiate a link between the claimed polynucleotides and any specific disorder. The specification merely discloses that the claimed polynucleotides are structurally related to GPCRs, and that they are expected to be

involved in neurotransmission (and thus, disorders). Many genes expressed in diseased tissues have nothing whatsoever to do with the disease and are not targets for drug development or toxicology. For example, actin and histone genes are expressed in diseased tissues; they are constitutively expressed in all tissues. These are not suitable targets for drug development or toxicology studies, since disruption of these genes would kill the patient.

Beginning at the last paragraph of p. 9 of the Brief, Appellants refer to the opinion of Dr. Bedilion that a person skilled in the art at the time of the invention would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays. Appellants refer to the opinion of Dr. Iyer, who explains in his declaration that a person of skill in the art in 1998 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays, and that to provide maximum versatility as a research tool, and as a biologist Dr. Iyer would want his microarray to include each newly identified gene as a probe. Beginning at the top of page 10, Appellants refer to the opinion of Dr. Rockett, who explains in his declaration that there are a number of other differential expression analysis technologies that preceded the development of microarrays, some by decades, and that have been applied to drug metabolism and toxicology research, and which are listed in the first paragraph. It is not disputed that one of ordinary skill in the art would agree that such differential expression analysis technologies including cDNA microarray technology are extremely valuable techniques, and that these were well-established utilities at the time of filing. However, the claims are not drawn to the various techniques or to a microarray. The claims are directed to a specific polynucleotide. Any polynucleotide that would be added to a microarray would increase the value of that microarray and possibly show altered expression due

to treatment with a potential drug target directed to a different polynucleotide (or the encoded protein), or be a part of a microarray that demonstrates differences in hybridization patterns in a particular disease state. Therefore, this asserted utility would be applicable to any polynucleotide and does not rely on any specific attribute of the polynucleotide, and thus the asserted utility for the particular polynucleotide claimed is not specific, substantial or well-established.

At the second paragraph on page 10 Appellants state that nowhere does the Patent Examiner address the fact that, as described on pages 31-32 of the Bandman '513 application, the claimed polynucleotides can be used as highly specific probes in for example, cDNA microarrays, and the claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine. The use of the claimed polynucleotide in microarrays was discussed in the first Office Action, Paper No. 9, at page 4, as not being a specific or substantial utility.

At p. 10 of the brief, Appellant argues that, given that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. Appellant reviews case law pertinent to the patentable utility of research tools. This is not found to be persuasive. Appellant's analogy is misplaced. It is true that a scale has patentable utility as a research tool. However, the object being weighed on the scale does not necessarily have patentable utility. In the instant case, microarray technology has patentable utility. However, the microarray is not being claimed, but rather a polynucleotide that can be used in microarrays. The claimed polynucleotide is not disclosed as being expressed at an altered level or form in any diseased

tissue as compared to the corresponding healthy tissue. Therefore, the assertion that the claimed polynucleotide has patentable utility as a probe in, or member of, a microarray is not specific. Any orphan polynucleotide can be used in the same way.

At pages 10-11, Appellants argue that literature reviews published shortly before the filing of the Bandman '513 application describing the state of the art further confirm the claimed invention's utility, and that Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated (Xenobiotica article, and Rockett Declaration, Exhibit C), and explains the recognition of the importance of differential gene expression and characterization, that differential expression technologies are applicable to a broad range of models and do not require any prior knowledge of the specific gene which are up or down regulated, and that the current use of gene profiling yields a pattern of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible in vivo similarities between the known and the standard, thus providing a platform for more extensive toxicological examination. On page 11, Appellants present another pre-September 1998 article, Lashkari et al., which explicitly states that predicted Open Reading Frames (ORFs) have numerous uses, such as by arraying onto glass for expression analysis. These are not persuasive. The Examiner notes that these references, e.g. Rockett et al. and Lashkari et al. have not been previously cited or discussed on the record, nor have they been made of record by appellants in any information disclosure statement. The Rockett et al. paper (Xenobiotica 1999, 2947):655-691), however, supports the Examiner's assertion that the use of the claimed nucleic acids in microarrays does not meet the requirement of being specific and substantial. In the abstract of the paper, Rockett et

al. state **"A important feature of the work of many molecular biologists is identifying which genes are switched on and off in a cell under different environmental conditions or subsequent to xenobiotic challenge. Such information has many uses, including he deciphering of molecular pathways and facilitating the development of new experimental and diagnostic procedures.'** (Emphasis added). In essence, Rockett is teaching that the purpose of such "open" microarrays, wherein the function of the specific nucleic acids is unknown, as is the case for SEQ ID NO: 7, is that the results of the experiment are to be used to decipher molecular pathways, and facilitate the development of other experimental or diagnostic procedures. Such would seem to the Examiner to clearly fall under the category of use for further experimentation to determine the properties of that which is being claimed, in this case the further experimentation being to develop other procedures that would take advantage of the knowledge gained by the initial experiment, or to 'decipher' molecular pathways. Thus, it is clear from Rockett et al. that, as asserted above by the Examiner, that the use of the claimed polynucleotide in either microarrays or in gene expression monitoring merely constitutes further research to determine the significance of the claimed nucleic acid itself; if the results of such experiments demonstrated that the claimed sequences were or were not present under particular conditions, such would be an invitation to experiment to determine why, which would fall under the aegis of further experimentation to determine the properties of that which is being claimed. Similarly, the Lashkari et al. publication, by appellant's admission a pre-filing date reference that has not been previously cited, does not support appellant's assertions: While Lashkari et al. indeed teach that "amplicons", or portions of DNA amplified from the genome by PCR can be used by arraying onto glass for expression analysis, the entire context of the article has been

ignored by appellants: The very first paragraph of the paper states "This massive and increasing amount of sequence information allows the development of novel experimental approaches to identify gene function." The paragraph bridging the columns of that page starts "Experimental analysis must be performed to thoroughly understand the biological function of a gene product." The same paragraph states "it is clear that novel strategies are necessary to efficiently pursue the next phase of genome projects- whole-genome experimental analysis to explore gene expression, gene product function, and other genome functions (emphasis added)." Thus, Lashkari et al. are clearly teaching that sequences of unknown function or significance are used in such strategies to learn more about the sequences themselves and the genes they represent. The Examiner maintains that this is clearly further research of the type that is not sanctioned as fulfilling the requirements of 35 U.S.C. § 101.

Similarly, Nuwaysir et al, newly cited and argued by Appellants, clearly shows that to be useful in a toxicology screen, one of ordinary skill in the art would want to know what kind of gene one was using; table 1, cited by appellants, clearly shows that one would first identify the function of the gene in the cell prior to using it in such a toxicology screen. No such identification has been performed for the nucleic acid of SEQ ID NO: 7.

B. The use of nucleic acids coding for polypeptides expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is alleged as "well-established".

Beginning at p. 12 of the Brief, Appellants argue that the claimed polynucleotides are useful as tools for toxicology testing, drug discovery, and the diagnosis of disease and that these

uses are "well-established". Each of these uses will be addressed individually, because the facts and issues directed to each use are distinct and separable. First, Appellant argues that toxicology testing is a well-established utility and concludes that the claimed polynucleotides could be used in this manner and that the claimed invention possesses utility, as described by Bedilion, Rockett and Iyer in their declarations, and cite a section on page 656 of the Rockett Declaration which explains that early identification of toxic drug candidates can shorten the development process and contribute substantially to the safety assessment of new drugs. Appellants also present two references, Nuwaysir et al. (reference 2) and Steiner and Anderson (reference 3) that teach the same, and cite Nuwaysir which describes a Human ToxChip containing 2089 human clones which were selected for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. On page 13 of the Brief Appellants argue that the more genes that are available for use in toxicology testing, the more powerful the technique and cite from Rockett and Dix (reference 4) that "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." Appellants also present an email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, was well as the original message to which she was responding (reference No. 5), indicating that even the expression of carefully selected control genes can be altered. Appellants also argue that there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

The e-mail referenced by appellants at page 13 of the Brief, also new to the prosecution, is not sufficiently legible to allow thorough analysis. However, it would seem to indicate that Ms. Afshari is in the process of designing chips to be used in toxicology screens, and is

performing substantially more characterization of the expression patterns of candidate sequences than is disclosed in the specification at hand. Thus, the e-mail would seem to indicate that while the nucleic acid of SEQ ID NO: 7 might be useful in a toxicology chip such as those allegedly designed by Ms. Afshari, it would require substantial further research to determine such. Utility must be in readily available form, and utility of SEQ ID NO: 7 in a toxicology screen does not appear to meet that burden. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct,.1966).

Appellants present sections of publications U.S. Pat. No. 5,569,588 (reference 9e), WO 95/21944 (reference 9a), WO 95/20681 (reference 9b) (5,840,484, 6,114,114, 6,303,297) and WO 97/13877 (reference 9g) are provided on pages 13-22 of the Brief, that allegedly provides further evidence of the well-established utility of all expressed polypeptides and polynucleotides in toxicology testing. On pages 13-15 of the Brief, Appellants present sections of WO 95/21944, which describes the use of microarrays in expression profiling analyses and that patterns of expression can be used to distinguish healthy tissues from diseased tissues and that patterns of expression can additionally be used in drug development and toxicology studies, without the knowledge of the biological function of the encoded gene product. On pages 15-18, Appellants present sections of WO 95/20681, which has three issued U.S. counterparts, U.S. Pat. Nos. 5,840,484, 6,114,114 and 6,303,297, which describes the use of transcript expression patterns, or images, each comprising multiple pixels of gene-specific information for diagnosis, for cellular phenotyping, and in toxicology and drug development efforts, using a plurality of methods for obtaining the expression data, one of which is microarray hybridization. On pages 18-20, Appellants present sections of U.S. Pat. No. 5,569,588, which describes an expression profiling platform, the "genome reporter matrix", which is different from nucleic acid microarrays, and

which also describes the use of nuclei acid microarrays and makes clear that the utility of comparing multidimensional expression datasets is independent of the methods by which such profiles are obtained, and that such expression analysis is useful in toxicology, particular pointing out that a gene's failure to change in expression level is a useful result. At the bottom of page 20, Appellants argue that the August 11, 1997 press release from the '588 patent's assignee, Acacia Biosciences (now part of Merck) (reference 9h), and the September 15, 1997 news report by Glaser in Genetic Engineering News (reference 9i), attest the commercial value of the methods and technology described and claimed in the '588 patent. On pages 21-22 of the Brief, Appellants present sections of WO 97/13877, which describes an expression profiling technology differing somewhat from the use of cDNA microarrays and differing from the genome reporter matrix of the '588 patent, but the use of the data is analogous. The reference describes use of expression profiling in toxicity determinations. On pages 22-23, Appellants state that the potential benefit to the public in terms of lives saved and reduced health costs, are enormous. Appellants provide evidence of the benefits of this information, in which CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology and other information to identify the key gene associated with Tangiers disease, and state that other customers have reduced the time associated with target discovery and validation, and that over 50 percent of the drug targets in its current pipeline of another customer were derived from the Incyte database, and by doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs. Appellants further assert that because the Examiner has failed to address or consider the "well-

established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

The references and arguments have been carefully considered but are not persuasive. For a utility to be "well-established" it must be specific and substantial. In this case, as indicated at pages 12-22 of the Brief, all nucleic acids and genes are in some combination useful in toxicology testing. However, the particulars of toxicology testing with the claimed polynucleotides are not disclosed in the instant specification. Neither the toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to the claimed polynucleotides. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed polynucleotide in an array for toxicology screening is only useful in the sense that the information that is gained from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array. Again, this is a utility which would apply to virtually ever member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Appellant's individual polynucleotides are affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polynucleotides have no "well-established" use. The artisan is required to perform further

experimentation on the claimed material itself in order to determine to what "use" any expression information regarding this nucleic acid could be put.

The supplied references and Appellants' arguments have been fully considered but are not deemed persuasive. As discussed above, the use of genomic information databases and microarray technologies are valuable and were well-established at the time of filing of the instant application. There is also no doubt that using such databases and technologies is very useful in discovering genes associated with diseases, or in drug discovery or toxicology testing. However, the utilities are well-established for entire databases or microarrays containing many polynucleotides, but the claims are drawn to specific polynucleotides, not the databases and techniques. The claimed polynucleotide has not been disclosed as being associated with any particular disease or condition by its being expressed at an altered level or form in diseased tissue as compared to the corresponding healthy tissue. Thus, this asserted utility is not specific. Determining the relationship between the claimed polynucleotides and any specific disease or disorder would require significant further research. Therefore, this asserted utility is also not substantial. In the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Because any polynucleotide could be used in the methods of the asserted utilities, the claimed polynucleotide does not have a specific, substantial and well-established utility. An analogous utility to that asserted by Applicants would be extracting mRNA from a tissue sample, electrophoresing the mRNA on a polyacrylamide gel, transferring to a membrane and hybridizing with a nucleic acid probe specific to that polynucleotide. It is well-established that any polynucleotide may be used in a method of hybridization to determine for example, the expression of the polynucleotide in various tissues, but this does not confer a well-established utility to the polynucleotide itself.

With regard to drug discovery and development, Appellants mention expression profiling as one use of the claimed polynucleotide. Appellants refer to recent developments as providing evidence that the benefits of this information are already beginning to manifest themselves. However, Appellant is incorrect in asserting that the efficacy (ability of producing a desired effect) of a compound could be evaluated from the result of a transcript image because there is no way to assess the meaning of any individual hit obtained from this procedure. The first requirement is that one must know the biological significance of the polynucleotide(s) which is (are) being evaluated. Without this information, the results of the transcript image are useless because one would not know if the polynucleotide expression should be increased or decreased or even what significance could be attributed to such changes in expression profiles.

With regard to diagnosis of disease, in order for a polynucleotide to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. The presence of a polynucleotide in tissue that is derived from cancer cells is not sufficient for establishing a utility

in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed cDNA and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. over expression). Evidence of a differential expression might serve as a basis for use of the claimed polynucleotides as diagnostics for diseases. However, in the absence of any disclosed relationship between the claimed polynucleotides or the proteins that are encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotides or the encoded proteins with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

C. The uncontested fact that the claimed polynucleotide encodes a protein in the GPCR family is also asserted to demonstrate utility.

At p. 22 of the Brief, Appellants argue that the utility of the claimed polynucleotide can be imputed based on the relationship between the protein of SEQ ID NO: 1, which has been

demonstrated is a member of the GPCR family, and that the GPCR family of proteins includes glutamate GPCRs that function in neurotransmission, and play a role in certain neurological disorders. Appellants state that the Patent Examiner does not dispute any of the facts set forth in the last full paragraph on page 22, or that if a polynucleotide encodes for a protein that has a substantial, specific and credible utility, then it follows that the polynucleotide also has a substantial, specific and credible utility. Appellants also assert on page 23 that the Examiner must accept the Applicant's demonstration that the polypeptide encoded by the claimed invention is a member of the GPCR family and that utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would double utility (*In re Langer*), and the Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary. Appellants also assert that the Examiner has not provided any evidence that any member of the GPCR family, let alone a substantial number of those members, is not useful, and in such circumstances, the only reasonable inference is that the polypeptide encoded by the claimed invention must be, like the other members of the GPCR family, useful.

The argument is not found to be persuasive, because evidence that a person of ordinary skill in the art would doubt utility in this case has been brought forth. Although the protein of the instant invention may be a G-protein coupled receptor, it is not predictable what the function of any GPCR protein is from this information. Whereas a broad class of enzyme such as the ligases have a general utility in such an application as ligation of DNA for cloning purposes and which is essentially applicable to all of the members of that class, the class of proteins known as G protein-coupled receptors do not have a common practical utility which is based upon a

property common to all of the members of that class. It is well known in the art that a certain class of dopamine receptor, for example, can be employed to identify agents useful in the treatment of Parkinson's disease whereas other classes of dopamine receptors can not. It is also well known that a nucleic acid encoding a particular dopamine receptor can be employed to identify individuals with a predisposition for alcoholism whereas a nucleic acid encoding any other dopamine receptor can not be employed in this capacity. Further, there is no support for an argument that identification of membership in the G protein-coupled receptor superfamily automatically confers a well-established utility, since members of this class bind to a large variety of different ligands and modulate vastly different physiological processes. Among related polypeptides in the GPCR family, structural similarity is not predictive of functional similarity. Each GPCR receptor or receptor-like protein responds to different ligands, mediates different signals and produces different responses in different cell types, and it is not predictable what the specific physiological function of a GPCR is based on structure. In the minireview of Ji et al., The Journal of Biological Chemistry, Vol. 273, No. 28, July 1998, pages 17299-17302, it is taught that the G protein-coupled receptor superfamily contains nearly 2000 members, which have the same basic structure, but are divided into subfamilies that bind different types of ligands, such as the biogenic amine receptors, nucleoside and nucleotide receptors, eicosaniod receptors, glycoprotein hormone-releasing hormone receptors, glucagons, calcitonin, vasoactive intestinal peptide receptors, parathyroid hormone receptors, protease activated receptors, glycoprotein hormone receptors and neurotransmitter receptors. Appellants assert that the protein of SEQ ID NO: 1 is a specific type of GPCR, that of being a metabotrobic glutamate receptor. However, There is no evidence presented in the specification that would categorize the

protein as being this type of receptor. The protein is identified as being a GPCR based on the protein having seven transmembrane domains, a structure which is conserved among all of the GPCRs. Even if the protein were classified as being a metabotrobic glutamate receptor, among the subclass of metabotropic receptors, there are five subtypes of receptor that have been identified (Watson and Arkinstall, (1991), The G-Protein Linked Receptor Facts Book, Academic Press, San Diego, CA., pp. 130-132). Watson and Arkinstall teach that these five receptor types differ in their agonist pharmacology and signal transduction pathways, and bind different agonists, such as quisqualate, ibotenate, ACPD and glutamate. Though the protein of the instant invention may be classified as a member of the GPCR superfamily, this does not automatically confer a specific and substantial utility to the protein, since there is extreme diversity in the activities and biological functions of these receptors. The M.P.E.P., 2107.01 states:

"A "specific utility" is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention."

The nucleic acids of the instant invention falls into this category.

D. Objective evidence is alleged to corroborate the utilities of the claimed invention.

Beginning at p. 23 of the Brief, Appellants argue that a "real-world" utility exists if actual use or commercial success can be shown. Citing case law, Appellant urges that such a showing is conclusive proof of utility. Appellant argues that a vibrant market has developed for databases

containing all expressed genes, including those of Incyte, the real party at interest in the instant appeal. Appellants urge that Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven valuable, and that the databases including the claimed polynucleotide would be even more valuable. Appellant's arguments have been fully considered but are not deemed to be persuasive. The case law indicates that a rejection under 35 U.S.C. § 101 *for lack of operability* can be overcome by a showing of actual use or commercial success. The instant issue is whether or not the asserted utilities meet the three-pronged test for credibility, specificity, and substantiality. Such is not necessarily addressed by a showing of commercial success or actual use. As argued previously, many products which lack patentable utility enjoy commercial success, are actually used, and are considered valuable. These include silly fads such as pet rocks, but also include serious scientific products like orphan receptors.

III. The patent examiner's rejections are alleged as being without merit

A. The precise biological role or function of an expressed polynucleotide is alleged as being not required to demonstrate utility

Beginning at p. 24 of the Brief, Appellant characterizes the examiner's rejection as being based on the grounds that, without information as to the precise biological role of the claimed invention, the claimed invention lacks specific patentable utility. Appellant characterizes the examiner's position as it is not enough that a person skilled in the art could use and would want to use the claimed invention either by itself or in a microarray, but that Appellant also is required to provide a specific and substantial interpretation of the results generated in a given expression analysis. Appellant argues that specific and substantial interpretations regarding biological

function may be required by technical journals, but are not necessary for patents. Appellants urge that the relevant question is not how or why the invention works, but whether the invention provides an identifiable benefit. Appellants argue that the present invention meets this test. Appellants argue that the threshold for patentable utility is low. Appellant urges that only throwaway utilities are insufficient, and that knowledge of biological function is not required. This is not found to be persuasive, as it mischaracterizes the examiner's position. The rejection never states that the precise biological role of a polynucleotide is required for it to possess patentable utility. If a polynucleotide is disclosed as being linked to a known disease or disorder, even if nothing is known or hypothesized about the activities of the encoded polypeptide, then the polynucleotide has patentable utility as a disease marker. However, if a specification does not disclose such information, as is the case here, then there is no patentable utility. If a compound causes the claimed polynucleotide to be expressed at a decreased level in a microarray, does that mean the compound is a potential drug or a potential toxin? That determination requires significant further research, and thus the asserted utility is not substantial. Also, any expressed polynucleotide *can* be used in a microarray; thus the unasserted utility is also not specific.

B. Membership in a class of useful products is asserted to demonstrate utility.

Beginning at p. 25 of the Brief, Appellants assert that the examiner improperly refused to impute the utility of the GPCR family to the claimed invention. Appellants urge that the case law requires only that the class not contain a substantial number of useless members. Appellant urges that the examiner has treated GPCRs as if the general class in which it is included is not

the GPCR family, but rather all polynucleotides or all polypeptides, and thus not pre-selected by nature to be useful. Appellants assert that while these "general classes" may contain a substantial number of useless members, the GPCR family does not. Appellants conclude that the examiner has not presented any evidence that the GPCR class of signaling molecules has any, let alone a substantial number, of useless members, and that the examiner must conclude that there is a "substantial likehood" that the protein of SEQ ID NO: 1 encoded by the claimed polynucleotide is useful. This is not found to be persuasive. The GPCR family is functionally highly diverse, as evidenced by the references made of record in the rejection and discussed under section II C. When there is great functional diversity in a structurally related class of compounds, the class cannot be used to predict a utility for a new compound that fits in the class by structural similarity. Such is the case here.

C. Because the uses of the claimed polynucleotide in toxicology testing, drug discovery, and disease diagnosis are asserted as practical uses beyond mere study of the invention itself, the claimed invention is alleged to have utility.

At p. 226-27 of the Brief, Appellants argue that the rejection is incorrectly based on the grounds that the use of an invention as a tool for research is not a substantial use. Appellants urge that only a limited subset of research uses are not substantial: those in which the only known use for the claimed invention is to be an object of further study, thus merely inviting further research. This is not found to be persuasive. As discussed above, whereas a scale or a microarray or a gas chromatograph has patentable utility as a research tool, the objects being evaluated with those research tools do not necessarily have patentable utility. In the instant case,

the claimed polynucleotide is not disclosed as having a specific activity, or having any property that can be specifically useful. The claimed invention is, in fact, the object of further study, merely inviting further research. None of the utilities asserted for the claimed polynucleotide meets the three-pronged test of being specific, substantial and credible.

D. The patent examiner is alleged to have failed to demonstrate that a person skilled in the art would reasonably doubt the utility of the claimed invention.

Beginning at p. 28 of the Brief, Appellants argue that the asserted utility for the polynucleotide encoding SEQ ID NO: 1 in the detection and diagnosis of follicular carcinoma of the thyroid based on a significant (4-fold) differential expression in that disease condition, is both specific, substantial and credible. Appellants urge that the gene of SEQ ID NO: 7 was most highly expressed in a thyroid follicular carcinoma library (THYRTUP02), was also expressed in a thyroid papillary carcinoma library (THYRTMT01) and was also expressed in a library associated with follicular adenoma (THYRNOT03), a precancerous condition to follicular carcinoma. The specification on page 35 states the sequence was not expressed in cytologically normal thyroid (5 libraries), lymphocytic thyroiditus (2 libraries), hyperthyroidism, goiter or papillary carcinoma. Appellants assert that such evidence provides more than a "substantial likelihood" that the polynucleotide may be used in the detection and diagnosis of disease, and that the evidence provided from the Northern analysis for SEQ ID NO: 7 supports applicants assertion for the use of the claimed polynucleotide in cancer as disclosed in the Bandman '513 priority application at pages 29-30. Appellants further assert that the Examiner's reliance on references such as the NCI guidelines for Marker Development to support her position is merely

an attempt to raise the standard to utility to one of near certainty, and the applicable standard in this case is not proof to certainty, but proof to reasonable probability.

This is not persuasive for many reasons. The abundance or presence of a gene in different libraries are not conclusive of the actual abundance or presence in an in vivo tissue. There are many reasons why one particular clone may be present in one library and not another, which has no bearing on in vivo abundance. For example, the GC content, or toxicity to the host may affect the levels of transcript found in libraries. Additionally, a cancerous cell line is not predictive of the situation in vivo. It is important to realize the key difference between cells derived from a primary source (such as a tumor) and established cancer cell lines. Whereas it is true that all cancer cells (whether from tumors or established cell lines) are immortal, the cells from freshly isolated tumors are phenotypically the same as the tumor from which they were isolated, whereas cells in established cell lines have undergone numerous phenotypic changes. The cells used in studies that are generated from freshly isolated tumors are kept alive on a short-term basis in cell culture (*in vitro*) for the screening processes. These cells are not established cell lines, which are kept alive in cell culture for a significant length of time, wherein cells with altered phenotypes emerge. Additionally, *only a single library* from each of the two cancerous and the one precancerous cell lines were analyzed. The presence of the polynucleotide in a single library of each type does not provide reasonable probability for the assertion that the polynucleotide can be used to detect and diagnose follicular carcinoma of the thyroid. Appellants' assertion the that Northern data provided in the Bandman '513 priority application further supports Appellants assertion for the use of the claimed polynucleotide in cancer is also not persuasive. Table 3 of Bandman,'513 application, demonstrates that the polynucleotide of

SEQ ID NO: 7 is expressed in reproductive, cardiovascular and gastrointestinal tissues, and that the disease or condition associated with the tissues are cell proliferation and inflammation, and pages 29-30 of the priority application state that the polynucleotides encoding HGPRP (which includes six different polynucleotides encoding different proteins) may be used for the diagnosis of disorders associated with expression of HGPRP, which includes more than thirty lines of listed diseases, so that the Bandman priority application does not provide evidence of a utility for a specific disease or disorder. Pages 4, 29, 30 and Table 3 of the Bandman priority application are included with the Examiner's Answer.

Applicants' Showing of Facts Allegedly Overcomes the Examiner's Concern That Applicants' Invention Lacks "Specific Utility".

Appellants on pages 28-29 of the Brief further assert that the submission of additional facts overcomes the concern that the asserted utility for the claimed polynucleotides is specific and substantial or a well established utility, and that each gene on a high density spotted microarray when probed provides a signal that is specific to the cognate transcript, and that each additional probe makes an additional transcript newly detectable by the microarray, increasing the detection range, and thus versatility, of the analytical device for gene expression profiling, and increasing the resolving power of the device. Applicants state on the record that the specificity of nucleic acid hybridization was well-established far earlier than the development of high density spotted microarrays in 1995, and indeed is the well-established underpinning of may, perhaps most, molecular biological techniques developed over the past 30-40 years.

This is not found to be persuasive. Any polynucleotide is a highly specific probe for itself or its complement, or any mRNA that can be transcribed from it. Such can be said for any polynucleotide. Thus, this asserted utility is not specific. Because any polynucleotide could be used in the methods of the asserted utilities, the claimed polynucleotide does not have a specific, substantial and well-established utility. An analogous utility to that asserted by Applicants would be extracting mRNA from a tissue sample, electrophoresing the mRNA on a polyacrylamide gel, transferring to a membrane and hybridizing with a nucleic acid probe specific to that polynucleotide. It is well-established that any polynucleotide may be used in a method of hybridization to determine for example, the expression of the polynucleotide in various tissues, but this does not confer a well-established utility to the polynucleotide, that is probed and detected by this method.

IV. By requiring the patent applicant to assert a particular or unique utility, it is alleged that the patent examination utility guidelines and training materials applied by the patent examiner misstate the law.

Beginning at p. 29 of the Brief, Appellant challenges the legality of the Patent Examination Utility Guidelines. Since an Examiner has no authority to comment on the legality of the Guidelines, this issue will be reserved for ruling by the Board of Patent Appeals and Interferences.

V. To the extent the rejection of the invention under 35 U.S.C. § 112, first paragraph, is based on the alleged improper rejection for lack of utility under 35 U.S.C. § 101, it is alleged that the rejection must be reversed

As Appellant indicates at p. 31 of the Response, a rejection under § 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under § 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967).

Therefore, for reasons set forth above, Appellants arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the *prima facie* case of lack of utility and it is believed that the rejections should be sustained.

The recited fragments and variants of SEQ ID NO: 1 and SEQ ID NO: 2 are asserted to be sufficiently described in chemical and structural terms that the skilled artisan would recognize applicants' possession of them at the time the application was filed.

On page 33, Appellants assert that with respect to the fragments of SEQ ID NO: 1, as recited in claim 1, Appellants submit that the recited fragments are disclosed in the specification and claims in terms of their specific amino acid sequences and therefore clearly meet the requirements for written description under 35 U.S.C. § 112, first paragraph. This is not persuasive, because even if the specific fragments were disclosed in the specification, the claims are not drawn to a cDNA ***consisting of*** a nucleic acid encoding those fragments, but are drawn to a cDNA ***comprising a*** nucleic acid encoding those fragments. Thus, the claims encompass a genus of nucleic acid molecules comprising a sequence encoding, for example, a fragment of 20 amino acids. Thus, the claims encompass virtually any random sequence of any length as long as it encodes the fragments recited in claim 1. The claims do not require that the nucleic acid molecules possess any particular biological activity or that the encoded protein possess any

particular biological activity. The specification has not described such a nucleic acid molecule except for the sequence of SEQ ID NO: 7.

On pages 33-35, Appellants assert that the homologues of SEQ ID NO: 1 referred to by the Examiner presumably relate to variants of SEQ ID NO: 1 and SEQ ID NO: 7, and submit that the polynucleotides and polypeptides including the variants are adequately described in accordance with 35 U.S.C. § 112, first paragraph and supported by relevant case law, and cite case law and the Patent and Trademarks Office's own "Guidelines for Examination of Patent Applications Under 35 U.S.C. Sec. 112, para. 1", published Jan. 5, 2001. Appellants argue that the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art, and that SEQ ID NO: 1 and SEQ ID NO: 7 are specifically disclosed in the priority application Serial No. 09/156,513, as are variants of the sequences, and that the chemical and structural features of SEQ ID NO: 1 are described, and given SEQ ID N): 1, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO: 1 having at least 90% sequence identity to SEQ ID NO: 1.

This is not found persuasive, because to provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of specific fragments or percent identity. As far as the claims encompass a nucleic acid sequence encoding a variant having a certain percent identity to SEQ ID NO: 1, there is not even identification of any particular portion of the

structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

A. The Specification allegedly provides an adequate written description of the claimed "variants" of SEQ ID NO: 1.

1. The present claims specifically define the claimed genus through the recitation of chemical structure.

Appellants assert that the Examiner's position that the subject matter is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is believed to present a misapplication of the law. On page 35, Appellants cite *Fiers v. Revel*, and argue that if a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, then a description also requires that degree of specificity. Appellants on pages 35-37 cite *University of California v. Eli Lilly and Co.,* and *Lilly*, and submit that in those cases, nucleic acids that were defined on the basis of potential methods of isolating DNA or functional characteristics did not comply with the written description requirement of 35 U.S.C. § 112, first paragraph, and assert that the claims at issue in the present application define polynucleotides and polypeptides in terms of chemical structure, rather than functional characteristics, and therefore the claims of the subject application are fundamentally different from those found in *Lilly* and *Fiers*. Appellants assert that there is no reliance merely on a description of functional characteristics of the polynucleotides or polypeptides recited by

the claims, and that by failing to base its written description inquiry "on whatever is now claimed", the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in Lilly and Fiers. These arguments are not found persuasive, because to provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof, which were considered and discussed in the analysis of the claims.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polypeptide sequence SEQ ID NO: 1, and discusses how variants may be obtained, and it cannot be established that a representative number of species have been disclosed to support the genus claim based on a single sequence.

2. The present claims allegedly do not define a genus which is "highly variant".

On pages 37-38, Appellants argue that the claims at issue do not describe a genus which could be characterized as highly variant, and submit the reference of Brenner et al. as evidence illustrating that the claimed genus is of narrow scope. Brenner teaches that 30% identity is a reliable threshold for establishing evolutionary homology between sequences aligned over at least 150 residues, and that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. Appellants argue that in accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as metabotropic GPCR proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO: 1, and the variant language of the present claims, recite for example, polynucleotides encoding "an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 41", and that this variation is far less than that of all potential metabotropic glutamate GPCR proteins related to SEQ ID NO:" 1. This is not considered persuasive, because claim 1 encompasses a cDNA comprising a nucleic acid encoding an amino acid sequence, for example, amino acids 156-175 of SEQ ID NO: 1. Therefore, the claim encompasses a cDNA comprising a nucleic acid that could encode a protein that only need comprise this 20 amino acid fragment, and if this protein were 441 amino acids in length, the percent identify would be only about 5% to that of SEQ ID NO: 1, and such a protein would be highly variant to the protein of SEQ ID NO: 1.

3. The state of the art at the time of the present invention is asserted to be further advanced than at the time of the Lilly and Fiers applications.

On page 38, Appellants assert that in the *Lilly* and *Fiers* cases, the parties claimed benefit of priority from 1977 and 1979, respectively, and thus the written description inquiry in those cases was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology. Appellants argue that the present application has a priority date of Sept. 17, 1998, and with the remarkable advances in recombinant DNA technology in the 20 or more years from the time of filing of the applications in *Lilly* and *Fiers*, one of skill in the art would recognize that, given the sequence information of SEQ ID NO: 1 and SEQ ID NO: 7, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application. This is not found persuasive because although recombinant DNA technology has advanced tremendously since the time of *Lilly* and *Fiers*, the case law pertaining to written description requirement still requires that to provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus, which factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. Because the instant application only discloses one polypeptide sequence, and the claims do not recite any function, the written description has not been met.

Summary

Appellants summarize their arguments on pages 38-39, which have been addressed in the response above.

The now claimed invention, at least as recited in claims 1 and 3-6, is allegedly supported by both a specific and substantial asserted utility and a well established utility that is disclosed and enabled in priority application Serial No. 09/516,513.

On pages 39-40, Appellants submit that for the reasons cited above in response to the rejection of claims under 35 U.S.C. § 101/112, the specification supports a specific and substantial asserted utility, as well as a well established utility for the claimed invention that is similarly disclosed in the priority application Serial No. 09/516,513, in accordance with 35 U.S.C. § 120, therefore providing an effective filing date for the instant application of Sept. 17, 1998. Applicants' arguments have been fully considered but are not deemed persuasive, for reasons of record in the previous Office Actions, Paper Nos. 9 and 11, and for the reasons discussed under 35 U.S.C. § 101 in the present action.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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